UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,610	10/08/2004	B. Wesley Trotter	21077YP	4061

210 7590 03/13/2007

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
JARRELL, NOBLE E	
ART UNIT	**PAPER NUMBER**
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,610	TROTTER, B. WESLEY	
	Examiner	Art Unit	
	Noble Jarrell	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *4* is/are allowed.

6)☒ Claim(s) *1-3 and 5-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/24/2005 and 4/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 are pending in the instant application and are being examined in the current office action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3 and 5-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some portions of formula I and cancer, diabetes, and hyperproliferative disorder, does not reasonably provide enablement for several portions of formula I and autoimmune disorder, aging, acromegaly, and Crohn's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. The factors are: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quality of experimentation needed to make or use the invention based on the content of the disclosure.

Only certain compounds and certain portions of formula I are enabled. The portion of formula I that is enabled is the central ring (the phenyl fused to the bicyclic nitrogen ring). This ring core is novel relative to the possible substituents coming off the ring. In addition, the free forms of the compounds from examples 1-4 are enabled. These compounds are: 3-(3 -bromobenzyl) -11 -methyl -1,2,3,4,5,6 -hexahydro -5,2-(epiminomethano)-3-benzazocine; 3-(3-bromobenzyl)-l,2,3,4,5,6-hexahydro-5,2-(epiminomethano)-3-benzazocine; 3,11 -bis(3-bromobenzyl)- 1,2,3,4,5,6-hexahydro-5,2-(epiminomethano)-3-benzaocine; and 11 -acetyl-3-(3-bromobenzyl)-1,2,3,4,5,6-hexahydro-5,2-(epiminomethano)-3-benzazocine. Of working examples 1-4, only example 2 is enabled currently because it has a correct name and structure.

The following portions of formula I are not enabled because the possibilities do not make any sense chemically. In formula I, substituent $(R^1)_s$ is attached to the phenyl ring that is part of the larger ring. Variable R^1 can be hydrogen and variable S is defined as 0-16 (line 25). The phenyl ring in formula I only has 4 possible site sites for substitution, therefore it is implausible for S to range from 0-16. In the second embodiment on page 7, S is defined as 0-6 (line 14). This range is also unreal because the phenyl ring only has 4 substitution sites. If R^1 is hydrogen, the carbons in the phenyl ring that are not fused to the nitrogen bicycle will have no substituents and therefore each have a formal charge of negative 1. This molecule cannot exist. Therefore, variable S should be amended to a range from 1-4 to allow for hydrogen to be attached to the ring carbons that are not fused. Another problem with formula I is three possibilities for variable X, $S(O)_mR^4$, $C(O)OR^4$, and $C(O)N(R^4)_2$ (page 5, lines 17-19). The last two groups mentioned are terminal groups and therefore cannot be embedded in a chain. If $C(O)OR^4$ is embedded in a chain, the single-bonded nitrogen will have a formal charge of positive 1 due to the fact that variable V is required to be in the chain. If $C(O)N(R^4)_2$ is part of the chain, the amide nitrogen will also have a formal charge of positive 1 because variable V is required to be in the chain. As for $S(O)_mR^4$ group, the sulfur atom will be dicationic because variable V has to exist in the chain. This is most likely the case, even if variable m is 0. The last problem with formula I is variable Q. If is greater than zero, the terminal atom that is part of non-chemically sound substituents of variable X will become even more charged. Any variations of formula I with these problems are not enabled because the molecules cannot exist.

On page 52, the R' chain is implausible as well. The R' chain, defined as $-(CR^{1a}{}_2)_{n-1}$-X-$(CR^{1a}{}_2)_p$-V-$(R^2)_q$, where variable n is defined 0-6, cannot exist. For values of n greater than 1, the chain is chemically sound. However, when n=0, the first carbon would be a chain of –1 carbons. That length of carbon chain cannot exist.

There are problems with example 1 (page 56), example 3 (page 61), and example 4 (page 62). Example 1 is named as a dichloride, however, in the structure, only 1 chloride ion is shown. Example 3 has the same problem as example 1. Example 4 requires two anionic charges to balance the dicationic charge, however the name only shows 1 trifluoroacetate ion present in the molecule and the structure itself only has 1 anion present as well. If the appropriate corrections are made, these compounds can be enabled in addition to example 2.

The following disorders from claim 10 are enabled because of their relationship to IGF-1R: cancer, diabetes, a hyperproliferative disorder, and acromegaly.

Applicants teach from assays completed that the example compounds inhibit the protein kinase IGF-1R. Only three of the disorders mentioned in claim 10 are enabled by the specification. The enabled disorders are each associated with increased expression of IGF-1R. As the expression increases, the severity of the hyperproliferative worsens. Since cancer can be considered a hyperproliferative disorder, it is also enabled. Acromegaly is enabled because IGF-1R stimulates cell growth and proliferation, which includes osteoblasts. Diabetes is enabled because defects of IGF-1R are associated with type II diabetes.

Applicant does not teach the correlation between IGF-1R and the following disorders: autoimmune disorders, aging, and Crohn's disease. The specification says that RTK's and CTK's are suspected in hyperimmune disorders, but that is not a guarantee. Aging is not enabled by the specification because the specification teaches that the life span of mammals is increased by lower levels of IGF-1R. That could be considered increasing the longevity of life, but certainly not aging. As for Crohn's disease, there is no mention of IGF-1R being involved with the treatment of small intestinal disorders.

One of ordinary skill in the art would have to prove that this enzyme is associated with the non-enabled diseases in some fashion. This step requires undue experimentation and it cannot be predicted from the specification whether or not that IGF-1R is associated with these disorders.

Given the problems with formula I, working examples, and diseases not being enabled, the whole invention cannot be enabled at this time.

4. Claim 1 has several problems. The first problem is the range of possible values for variable S. Variable S can range from 0-16. Given that the fused phenyl ring only has 4 open substitution sites, the maximum value for the variable can be 4. In addition, variable R^1 can be hydrogen. If R^1 is hydrogen and S equals 0, the ring carbons of the phenyl ring would all formal charges of negative one. A tetraanionic molecule is not stable as is, and when the anionic charge is on a phenyl ring that is already electron rich cannot exist. Therefore, variable S should be defined as 1-4. The next problem with formula is three possibilities of variable X. The three possibilities of variable X that do not make sense chemically, given other factors, are $S(O)_mR^4$, $C(O)OR^4$, and $C(O)N(R^4)_2$ (page 69, lines 21-23). The last two groups mentioned are terminal groups and therefore cannot be embedded in a chain. If $C(O)OR^4$ is embedded in a chain, the single-bonded nitrogen will have a formal charge of positive 1 due to the fact that variable V is required to be in the chain. If $C(O)N(R^4)_2$ is part of the chain, the amide nitrogen will also have a formal charge

of positive 1 because variable V is required to be in the chain. As for $S(O)_mR^4$ group, the sulfur atom will be dicationic because variable V has to exist in the chain. This is most likely the case, even if variable m is 0. The last problem with formula I is variable Q. If is greater than zero, the terminal atom that is part of non-chemically sound substituents of variable X will become even more charged. Compounds with these types of problems cannot be made, and are therefore not enabled.

Allowable Subject Matter

6. Claim 4 contains allowable subject matter. These four compounds are free of the prior art of record, and are therefore novel and patentable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on Monday-Friday from 7:30-5:00. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NJ

VICKIE KIM
PRIMARY EXAMINER